Venous Thromboembolism After Acute Stroke

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Background—Treatment for venous thromboembolism (VTE) is highly effective in preventing morbidity and mortality, yet pulmonary embolism (PE) accounts for up to 25% of early deaths after stroke. This is because the current diagnostic paradigm is reactive rather than proactive: the clinician responds to VTE when it becomes symptomatic, in the expectation that initiation of treatment will prevent progression to more serious manifestations. This approach is flawed, because sudden death from PE is frequently unheralded and nonfatal symptomatic pulmonary emboli are often unrecognized or misdiagnosed.

Summary of Comment—Morbidity and mortality from PE could be reduced either by more effective thromboprophylaxis or earlier diagnosis and treatment of established VTE. The fact that early use of short-term, low-dose, unfractionated heparin (UFH) is not associated with sustained, clinically meaningful benefit suggests that a fundamental change in the diagnostic approach to VTE is needed, one which requires a greater appreciation that clinically apparent events are merely the tip of the thromboembolism iceberg.

Conclusions—Research into a strategy of screening for subclinical VTE in these patients is needed, with a view to identifying a subgroup at risk of progression to symptomatic and life-threatening events, in whom outcome might be improved by anticoagulation. (Stroke. 2001;32:262-267.)

Key Words: cerebral infarction ■ deep vein thrombosis

In this article, an overview of data is presented on the incidence and natural history of venous thromboembolism (VTE) after stroke. Strategies of thromboprophylaxis, the morbidity and mortality associated with established VTE, and the risks of anticoagulant use in acute ischemic stroke are also discussed. It is argued that a strategy of screening for subclinical deep vein thrombosis (DVT) is required, though a further trial of thromboprophylactic low-dose, low-molecular-weight heparin (LMWH) may still be justified.

Incidence of DVT After Stroke

Studies with 125I fibrinogen screening in patients with acute hemiplegic stroke have shown an incidence of DVT of approximately 50% within 2 weeks in the absence of heparin prophylaxis; the majority of these affect the paralyzed leg and are asymptomatic.1 Approximately two thirds of these are below-knee DVTs,2 in contrast to unselected (nonstroke) patients presenting with symptomatic DVT, in whom the majority are proximal.3 DVTs develop as early as the second day, with the peak incidence between days 2 and 7.1 The risk of DVT correlates with the degree of paralysis4 and is greater in older patients5 as well as those who have atrial fibrillation.6 Predilection for the paralyzed leg is probably explained by a combination of loss of the calf muscle pump and repeated minor trauma.7

DVT is also present in a significant proportion of patients during the rehabilitation phase of stroke, the risk being greater in those who are more immobile: in a study of 150 patients admitted to a stroke rehabilitation unit at, on average, 9 weeks after stroke, bilateral venography revealed DVT in 33%.8

Clinical Significance of Asymptomatic Proximal DVT After Stroke

The main clinical significance of asymptomatic proximal DVT is its potential to cause fatal pulmonary embolism (PE). Indeed, the majority of symptomatic PEs in unselected patients are unheralded and arise from previously subclinical DVT.9 In a study of unselected patients performed before anticoagulants were in routine use, untreated, clinically apparent DVT was associated with a mortality from PE of up to 37%.10 The risk of fatal PE associated with untreated subclinical DVT is lower, though it remains significant. Early studies in patients with hip fractures found the risk to be around 10%,11,12 but a more recent overview in postoperative patients has suggested that predominantly subclinical DVT diagnosed by 125I fibrinogen scanning is associated with a 5% risk of fatal PE.13,14 Although there are few data on the natural history of untreated subclinical DVT in stroke patients, in one study patients with proximal subclinical DVT had a 35% risk of clinical PE.15

Fatal pulmonary emboli usually arise from proximal DVT,16 which accounts for one third of all DVTs in surgical
patients.\textsuperscript{17} If it is assumed that the 5% of postoperative patients with untreated subclinical DVT who die from PE have proximal DVT, then 15% of subclinical proximal DVTs result in fatal PE. Three percent of stroke patients succumb to PE within 3 months,\textsuperscript{18} a mortality confined to the half who develop DVT.\textsuperscript{4} Because one third of these DVTs are proximal\textsuperscript{2} and most are silent,\textsuperscript{1} the data suggest that the mortality associated with untreated proximal subclinical DVT after stroke is some 15%, which is similar to that in postoperative patients.

A secondary concern is the potential to cause the post-thrombotic syndrome, characterized by persistent pain and swelling, with or without venous ulceration.\textsuperscript{19} The incidence of this disorder approaches 90% in patients with untreated symptomatic DVT.\textsuperscript{10} Although it is recognized that many patients who present with this syndrome have no history of clinical VTE (the entire process having been clinically silent),\textsuperscript{20} the incidence after untreated asymptomatic DVT is unknown. The long-term incidence in patients with symptomatic, treated proximal DVT is approximately 30%; however, there are conflicting data as to whether it occurs in patients with adequately treated asymptomatic proximal DVT.\textsuperscript{21,22}

**Clinical Significance of Asymptomatic Below-Knee DVT After Stroke**

A major concern in patients who have untreated below-knee DVT is the 20% risk of proximal extension,\textsuperscript{23} a subgroup that cannot accurately be predicted on clinical grounds.\textsuperscript{24} Clinical PE can, however, occur even in the absence of propagation,\textsuperscript{16,25} and routine ventilation-perfusion (VQ) scanning demonstrates silent PE in up to one third of patients who have isolated below-knee DVT.\textsuperscript{26,27} Although pulmonary emboli arising from below-knee DVTs are more likely to be small and asymptomatic and therefore less likely to be life threatening than those associated with proximal DVT,\textsuperscript{28,29} the risk of fatal PE attributable to untreated, nonpropagating below-knee DVT has not yet been defined. Symptomatic, isolated, below-knee DVT may cause the postthrombotic syndrome,\textsuperscript{29} but it is unclear whether this entity is a sequela in asymptomatic cases.

**Clinical Significance of Pelvic Vein Thromboses After Stroke**

Pelvic vein thromboses may account for a significant minority of pulmonary emboli in unselected (nonstroke) patients: in a series of 353 autopsies of patients in whom pulmonary emboli were found, the pelvic veins accounted for 11.5% and the inferior vena cava 5% of the identifiable sources of emboli.\textsuperscript{30} However, the incidence and clinical significance of isolated pelvic and inferior vena cava thromboses after stroke is unknown, because these have not been detected by \textsuperscript{125}I fibrinogen scanning,\textsuperscript{31} the main screening tool used in early studies investigating the incidence of DVT after stroke.\textsuperscript{1}

**Incidence of PE After Stroke**

The incidence of clinical PE reported in the absence of heparin prophylaxis has varied considerably, depending on the methodology of the studies. In the International Stroke Trial (IST), the incidence was 0.8% at 2 weeks.\textsuperscript{32} Similarly, in a retrospective study of 607 patients who had acute stroke, PE was reported in 1% during the period of hospitalization.\textsuperscript{33} However, prospective studies that focused specifically on venous thromboembolic complications reported incidences of clinically apparent PE of 10% to 13% (excluding pulmonary emboli identified at autopsy that were asymptomatic during life).\textsuperscript{15,34} These data strongly suggest underascertainment in studies reporting much lower incidences of PE.

The risk of PE also extends into the rehabilitation phase. In a retrospective study of 363 patients who did not receive heparin prophylaxis and entered a rehabilitation unit 4 weeks after stroke, 4% developed PE (confirmed by VQ scanning) on average 11 days after entering the unit.\textsuperscript{35}

Only 1 small study has prospectively screened for PE by using VQ scintigraphy. Dickmann et al\textsuperscript{36} studied a group of 23 patients 10 days after hemorrhagic stroke and found evidence of PE in 39%, though the proportion with symptoms was not stated. Autopsy studies show that half of the patients who die in hospital after the first 48 hours poststroke have evidence of PE,\textsuperscript{15,37} which suggests that pulmonary emboli are often subclinical and/or unrecognized after stroke.

**Morbidity and Mortality Due to PE After Acute Stroke**

Pulmonary emboli account for 13% to 25% of early deaths after stroke.\textsuperscript{38–40} Although they may occur as early as day 3,\textsuperscript{41} fatal emboli are unusual in the first week\textsuperscript{40} and are most frequent between the second and fourth weeks, when they are the most common cause of death.\textsuperscript{18} Those more severely disabled are most likely to be affected,\textsuperscript{42} but PE may also occur in ambulatory patients.\textsuperscript{18}

The mortality attributed to untreated clinical PE in unselected (nonstroke) hospitalized patients is approximately 30%.\textsuperscript{43} However, PE in stroke patients may have a higher mortality than that in other clinical settings\textsuperscript{15,41,44}; in one series of stroke patients, half of the clinical pulmonary emboli presented as sudden death.\textsuperscript{44} The morbidity associated with nonlethal pulmonary emboli should not be overlooked; this may manifest primarily as impaired cardiorespiratory reserve adversely affecting rehabilitation and potentially influencing functional outcome.\textsuperscript{45}

**Difficulties in Diagnosis of Symptomatic PE After Acute Stroke**

The signs and symptoms of PE are notoriously nonspecific,\textsuperscript{46} and both underdiagnosis and misdiagnosis are well documented, particularly in the elderly.\textsuperscript{47,48} A number of factors make diagnosis even more difficult in poststroke patients, a group in whom antemortem diagnosis is especially poor.\textsuperscript{39} Patients may not complain of symptoms because of dysphagia, cognitive impairment, or mental obtundation.\textsuperscript{49} In addition, pneumonia, the illness for which PE is most often mistaken,\textsuperscript{47} is also a common complication after stroke.\textsuperscript{18} This can lead to misdiagnosis, particularly as it may be underappreciated that up to two thirds of patients with PE develop fever.\textsuperscript{50} Indeed, pneumonia and PE can commonly occur together, but the possibility of coexistent PE in a patient with strong clinical evidence of pneumonia is rarely considered; in a postmortem series of unselected patients found to
have PE, pneumonia coexisted in 40%, though PE had not been diagnosed antemortem in any of the patients who had pneumonia. Finally, elderly patients with stroke may not be extensively investigated, and subtle clinical signs of PE, such as an asymptomatic mild increase in respiratory rate, are easily overlooked.

Stroke patients with suspected PE will usually undergo VQ scanning as the imaging modality of first choice. The importance of integrating this information with an assessment of the clinical probability of PE, either derived subjectively or by using scoring systems, has been stressed.9,52

Subclinical VTE
Clinically manifested disease represents the tip of the thromboembolism iceberg.53 Screening studies in both stroke and postoperative patients,1,11,17 together with the low incidence of symptomatic DVT in patients with PE,9 demonstrate that the majority of DVTs are asymptomatic. Screening patients with symptomatic proximal DVT without clinical evidence of PE reveals evidence of subclinical PE in up to half.54 Furthermore, VQ scanning in predominantly asymptomatic postoperative patients reveals pulmonary emboli in 12% to 18%.55–57 Clearly, only a small proportion of pulmonary emboli produce symptoms.

Treatment of Established VTE
Treatment of symptomatic VTE is highly effective in reducing morbidity and mortality. In an overview of 25 studies, recurrent fatal PE during a 3-month period of full anticoagulation occurred in only 1.5% and 0.4% of patients presenting with PE and DVT, respectively.58 In a meta-analysis of 13 trials comparing unfractionated heparin (UFH) with LMWH in the initial treatment of VTE, LMWH was found to be at least as effective as UFH and was associated with a significantly lower mortality.59

Although the need for anticoagulation in patients with symptomatic PE or proximal DVT is clear, the treatment of patients with symptomatic below-knee DVT is debated. The current consensus is that these patients should be either fully anticoagulated or followed up with serial noninvasive testing for 14 days,60 an approach shown to be safe in the absence of proximal extension.61–63 Optimal management of subclinical DVT has not been studied, but sensible conclusions can be drawn from a knowledge of the natural history of untreated DVT and the risks associated with anticoagulation, as discussed below.

Risks Associated With Anticoagulation in Acute Stroke
Analysis of data from the IST allows a comparison of the effect of medium-dose heparin (12 500 U of UFH twice daily), initiated within 48 hours of ischemic stroke and continued for 2 weeks, to no heparin on a number of end points. Although this dosing regime reduced the risk of PE and recurrent ischemic stroke, the reduction was more than offset by an increased risk of hemorrhagic stroke transformation and extracranial hemorrhage. Overall, there was an excess risk of death or recurrent stroke and major nonfatal extracranial bleeds of 0.5% and 1.5%, respectively, during the treatment period.32 White et al64 studied the risk of warfarin-related complications in 22 000 unselected patients diagnosed with DVT over a 3-month period. In the subgroup of 1312 patients with a history of stroke, the readmission rate due to bleeding was 1.7%. In a comparison cohort of patients hospitalized because of pneumonia or cellulitis without DVT, this figure was 0.7%, which suggests that the excess risk attributable to warfarin in the stroke subgroup was 1.0%. The excess risk of intracranial hemorrhage in this subgroup was not specifically studied, though it was 0.1% in the group as a whole.

The balance of risks might therefore favor initiation of anticoagulation in established VTE after stroke, where the risk of major morbidity or mortality associated with untreated DVT exceeds about 3%, the combined risk of death, recurrent stroke, and major bleeding associated with a few days’ treatment with heparin followed by 3 months of warfarin after acute ischemic stroke. This suggests that patients with subclinical proximal DVT would benefit from treatment. The balance of risks is less clear for nonpropagating, below-knee DVT, though this may be affected by factors such as inadequate cardiorespiratory reserve, because even a small PE can be fatal in such patients.65

Most clinicians would now initiate treatment with LMWH rather than UFH. Although LMWH is associated with a lower risk of hemorrhage in medical patients,66 data comparing LMWH and UFH in stroke patients are insufficient to draw conclusions about their relative safety in this context.67 In addition, most diagnoses of clinical VTE are made several days after stroke onset,40,41 by which time the risk of hemorrhagic stroke transformation, greatest in the first 4 days, is likely to be lower.68 This approach might be associated with a more favorable risk-to-benefit ratio.

Heparin Thromboprophylaxis After Stroke
Prophylactic use of UFH in surgical patients reduces the incidence of DVT, PE, fatal PE, and total mortality.13 and LMWH is at least as effective.69 An overview of 10 trials of prophylactic UFH or LMWH in more than 1000 patients with ischemic stroke has shown an approximate 80% reduction in the incidence of DVT as detected by 125I fibrinogen scanning or venography, though the numbers were too small to draw firm conclusions about the effect on the incidence of PE and total mortality.70 In a recent Cochrane review71 of 13 trials of anticoagulants in acute stroke, fatal and nonfatal PE were found to be significantly reduced by 39%; however, it should be noted that these trials were heterogenous and included a mixture of low- and medium-dose anticoagulant regimes.

In the IST, treatment with low-dose heparin (5000 U of UFH subcutaneously twice daily) significantly reduced the combined risk of death and recurrent stroke at 14 days from 12% to 10.8%, an effect attributable predominantly to a reduced risk of recurrent ischemic stroke, as PE was not significantly reduced. Increases in the incidence of intracranial hemorrhage and of fatal or transfusion-requiring extracranial bleeds did not reach significance with this regime and are illustrated in the Table.32 Nevertheless, no reduction in overall mortality or disability could be demonstrated at 6 months, and routine use of heparin prophylaxis after stroke...
Effects of Low-dose UFH (5000 units BD) and Aspirin (300 mg OD) on End Points at 14 Days in the IST

<table>
<thead>
<tr>
<th></th>
<th>Aspirin + Low-Dose UFH</th>
<th>Aspirin, No UFH</th>
<th>No Aspirin, No UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.8%</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Transfused or fatal extracranial bleeds</td>
<td>0.8%</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>2.1%</td>
<td>3.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.5%</td>
<td>0.7%</td>
<td>0.9%</td>
</tr>
</tbody>
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has therefore not been recommended subsequent to this trial. One reason that the short-term benefit of low-dose UFH was not sustained may be that treatment was given for only 2 weeks, because most fatal PEs occur between the second and fourth weeks after stroke. In addition, there was no information given as to how DVTs and PEs were diagnosed, so that underascertainment may have occurred. A further trial of low-dose heparin (preferably LMWH) for an extended period and with a more systematic reporting of VTE may therefore be justified.

Other Strategies to Prevent VTE After Stroke
Graded elastic compression stockings are frequently used after stroke and have been shown to reduce the risk of DVT in surgical patients by about two thirds, though there are insufficient data to reach a definite conclusion about their effect on PE. Data are also lacking on their effectiveness in the context of stroke, or in combination with prophylactic-dose heparin, and they may be less acceptable to patients than subcutaneous heparin.

Intermittent pneumatic compression is effective in preventing DVT in general surgical and neurosurgical patients as well as in patients undergoing elective knee and hip replacement, in whom it probably has an effect comparable in magnitude to that of LMWH. However, there have been no large studies in medical patients.

Aspirin reduces the risk of VTE in surgical patients by at least one third, though it does not reduce overall mortality. In the International Stroke Trial, the incidence of fatal and nonfatal PE at 2 weeks was 0.6% in those treated with aspirin compared with 0.8% in controls, an effect that did not reach significance.

The Case for a More Anticipatory Approach to VTE Diagnosis After Stroke
Many pulmonary emboli that occur after stroke present as sudden death. Because the treatment for VTE is highly effective, the current expectant approach to its diagnosis, particularly in the absence of heparin prophylaxis, should be questioned. A strategy of screening for VTE in these patients therefore warrants evaluation.

Methods of Screening for DVT After Stroke
The choice of screening tool for DVT is problematic, because it would have to be noninvasive, inexpensive, and highly sensitive. Doppler ultrasound is a powerful technique for detecting symptomatic proximal DVT. However, combined data from 11 studies in high-risk postoperative patients indicate that the sensitivity for the diagnosis of asymptomatic proximal DVT is only 62% and that for asymptomatic below-knee DVT 48%. Although thrombi missed with ultrasound screening tend to be smaller and nonocclusive, it has been suggested that the technique may be unsatisfactory as a screening tool since many DVTs will not be detected. The utility of the technique for the detection of asymptomatic DVT after acute stroke has not specifically been evaluated.

The 125I fibrinogen test is no longer used because of the risk of transmission of infection with injected fibrinogen and impedance plethysmography is not useful for the detection of calf vein thromboses or asymptomatic DVT. Contrast venography remains the gold standard for diagnosing lower limb DVT, but would not be suitable because it is invasive and associated with a small risk of complications.

MRI is noninvasive and allows simultaneous imaging of the venous system in both lower limbs. In addition, pelvic vein and inferior vena cava thromboses are accurately identified, an important advantage over other techniques. MR venography compares favorably with contrast venography for the diagnosis of symptomatic proximal DVT but has not been evaluated for the diagnosis of asymptomatic DVT. More recently, MR direct thrombus imaging has shown excellent sensitivity and specificity for the diagnosis of asymptomatic above- and below-knee DVT. This technique allows direct visualization of thrombi so that equally favorable results might be expected in asymptomatic patients. Although availability is currently limited, MR technology is likely to play an increasingly important role in DVT diagnosis in the future.

D-dimers as a Screening Tool for DVT After Stroke
D-dimers are a cross-linked fibrin breakdown product generated from the degradation of the fibrin matrix of fresh venous thromboemboli. For symptomatic DVT or PE in unselected patients, ELISA assays have been shown to have an average diagnostic sensitivity of 97% at a threshold of 500 ng/mL, though the specificity is only 35% to 45%.

Harvey et al investigated the utility of a D-dimer assay as a screening test for subclinical DVT in 105 patients who were, on average, 25 days poststroke and found that a threshold of 1092 ng/mL had a sensitivity of 100% and specificity of 66% for diagnosing DVT as detected by Doppler ultrasound. Although this study suggests that D-dimers may have a useful screening role, allowing the identification of a subgroup of patients who should undergo targeted imaging, the results cannot be extrapolated to patients in the first few days after stroke, because acute nonlacunar ischemic stroke increases D-dimer levels. Decay to baseline occurs over the next 30 days, so the normal range differs in the acute and rehabilitation settings.

A D-dimer threshold useful in the rehabilitation phase may therefore not be discriminatory in the first few days after stroke, the period during which most DVTs develop. It should also be noted that although several commercial D-dimer assays are now available, results from studies with
one manufacturer’s test cannot necessarily be extrapolated to another.93 Further studies are required to examine the utility of D-dimers as a screening test for DVT in acute stroke.

Conclusions
The morbidity and mortality attributable to VTE after stroke is unlikely to change with a perpetuation of current practice. As one of the most eminently treatable of stroke complications, and in the absence of more effective prophylaxis, research is needed into the development of noninvasive strategies of screening for subclinical DVT in these patients. Examples of future studies might include the assessment of MR technology, investigation of Doppler ultrasound for the diagnosis of subclinical proximal DVT, and the evaluation of D-dimers as a possible discriminator of DVT status in acute stroke, potentially facilitating targeted imaging in a subgroup with a high risk of underlying DVT.

Although optimal treatment of subclinical DVT after stroke is currently unknown, extrapolation of current evidence would suggest that the benefits of anticoagulation outweigh the risks associated with untreated subclinical proximal DVT. However, the balance of risks might generally favor an expectant approach in patients with adequate cardiorespiratory reserve who have isolated below-knee DVT, with repeat imaging to identify the subgroup in whom proximal propagation occurs.

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